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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/804,954	03/19/2004	Marise S. Gottlieb		8077

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EXAMINER	
CORDERO GARCIA, MARCELA M	
ART UNIT	PAPER NUMBER
1654	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/804,954	GOTTLIEB, MARISE S.	
	Examiner	Art Unit	
	MARCELA M. CORDERO GARCIA	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 March 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4 and 6-18* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4, 6-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

Claims 1-4, 6-18 are pending in the application. A 37 CFR § 1.132 declaration filed on 1/7/08 was previously considered by Examiner (see Advisory Action, dated 2/8/08). A copy of this 37 CFR § 1.132 was submitted again on 3/5/08.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 5 March 2005 has been entered.

Claims 1-4, 6-18 have been rejoined, the restriction requirement issues on 9 May 2006 has been withdrawn because the claims as amended now present overlapping subject matter. Claims 1-4, 6-18 are presented for examination on the merits.

Any previous rejection, which is not further restated herein, is withdrawn.

Sequence Compliance

Applicant is advised that the application is not in compliance with 37 CFR §§ 1.821-1.825.

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 CFR

§§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. Applicant must comply with the requirements of the sequence rules (37 CFR §§ 1.821- 1.825) in order to completely respond to this office action.

Specifically, no sequence listing / CRF have been provided which includes the amino acid sequences presented e.g., in page 7, lines 13-14. In order to satisfy the sequence rules requirements, Applicant needs to provide an amendment to the instant claims and specification to include reference to the appropriate "SEQ ID NO:".

In case of any new sequences not properly identified in the instant specification, Applicant is required to provide a substitute computer readable form (CRF) copy of a "Sequence Listing" which includes all of the sequences that are present in the instant application and encompassed by these rules, a new or substitute paper copy of that "Sequence Listing", an amendment directing the entry of that paper copy into the specification, and a statement that the content of the paper and computer readable copies are the same and, where applicable, include no new matter, as required by 37 C.F.R. § 1.821(e) or 1.821(f) or 1.821(g) or 1.825(d). The instant specification will also need to be amended so that it complies with 37 C.F.R. § 1.821(d) which requires a reference to a particular sequence identifier (SEQ ID NO:) be made in the specification and claims wherever a reference is made to that sequence. For rules interpretation Applicant may call (703) 308-1123. See M.P.E.P. 2422.04.

Please direct all replies to the United States Patent and Trademark Office via one (1) of the following:

1. Electronically submitted through EFS-Bio (<http://www.uspto.gov/ebc/efs/downloads/documents.htm>, EFS Submission User Manual - ePave)

2. US Postal Service:
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Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 6-18 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Enablement is considered in view of the Wands factors (MPEP 2164.01(a)).

Nature of the invention. The claims are drawn to methods of controlling chronic inflammation associated with the Metabolic Syndrome in an individual having the Metabolic Syndrome, comprising: administering to said individual an effective dosage of a pharmaceutical composition selected from the group consisting of YG-Product, YGG-Product, Purified Leukocyte Dialysate Subfraction, and a combination thereof.

State of the prior art. At the time the invention was made, WHO in 1998 outlined a provisional classification of diabetes that included a working definition of the metabolic syndrome, as follows:

Insulin resistance, identified by 1 of the following: type 2 diabetes or impaired fasting glucose or impaired glucose tolerance or for those with normal fasting glucose levels (<110 mg/dL), glucose uptake below the lowest quartile for background population under investigation under hyperinsulinemic, euglycemic conditions. Plus any of 2 of the following: Antihypertensive medication and/or high blood pressure (≥ 140 mmHg systolic or ≥ 90 mm Hg diastolic), plasma triglycerides ≥150 mg/dL , HDL cholesterol < 35 mg/dL, BMI > 30 kg/m2 or waist:hip ratio > 0.9 men, > 0.85 women, urinary albumin excretion rate > 20 ug/min or albumin: creatinine ratio ≥ 30 mg/g. (see, e.g., Grundy et al., see pages 433-438, especially page 435).

Breadth of the claims. The claims are extremely broad, encompassing treatment of any chronic inflammation associated with Metabolic Syndrome.

Working examples. Example 1 discloses data from a clinical trial in patients with HIV Disease (not a Metabolic Syndrome) using YG and YGG. The HIV patients develop a lipodystrophy with features very similar to the Metabolic Syndrome. Correction of immune deficiency or disregulation with the unique immunoregulators described herein appears to correct key components of the metabolic syndrome and lipoatrophic diabetes mellitus associated with HIV disease. Based on the findings, Applicant concludes that is possible to treat patients who have or who are at risk for the Metabolic Syndrome with one or more of the immunoregulators instantly claimed and thus prevent

the diabetes mellitus, coronary heart disease, cancer and other outcomes associated with the metabolic syndrome. Example 2 is a prophetic example drawn to a industrial exposure of YG administration in order to increase DH responsiveness and decrease C-Reactive Protein. Example 3 is drawn to a prophetic example involving exposure to jet fuel and YGG. Example 3 is drawn to a prophetic example of a patient treated for HIV disease who has abnormal glucose tolerance and is therefore treated with YG product, therefore preventing diabetes type 2, coronary heart disease. Example 4 is drawn to a prophetic example of a woman with a weight gain of 50 pounds, high blood pressure, vaginal pruritis and who lives near an oil refinery. She is found to have impaired glucose tolerance, elevated serum triglycerides, low HDL and high LDL receptors and high C-Reactive Protein and fibrinogen levels, along with candida infection. YG sublingual taken once every two weeks and their risk of diabetes mellitus and coronary heart disease is reduced.

Guidance in the specification. The specification provides little guidance regarding practice of the claimed methods. The specification refers generally to the metabolic syndrome associated symptoms and teaches prevention of diabetes mellitus, coronary heart disease and other outcomes, however, it does not produce any corroborating evidence with regards to patients actually having metabolic syndrome.

Predictability of the art. The physiological art in general is acknowledged to be unpredictable (MPEP 2164.03). In the instant application, Applicants have not clearly demonstrated that the instantly claimed YG products, YGG and so forth can actually prevent and/or treat metabolic syndrome and chronic inflammation associated with it,

rather, the one working example is drawn to alleviating metabolic-syndrome-like symptoms in AIDS patients (see Example 1).

Amount of experimentation necessary. Grundy et al. teaches that regardless of diagnostic criteria used, there is full agreement that therapeutic lifestyle change, with emphasis on weight reduction, constitutes first line therapy for metabolic syndrome. Drug treatment to directly reduce insulin resistance is promising, but clinical trials to prove reduction of CVD are lacking. In patients in whom lifestyle changes fail to reverse risk factors, consideration should be given to treating specific abnormalities in these risk factors with drugs. Use of drugs to target risk factors should be in accord with current treatment guidelines (Grundy et al., page 438). As previously pointed out, the metabolic syndrome is drawn to a constellation of symptoms: atherogenic dylipidemia, elevated blood pressure, prothrombotic state, proinflammatory state and hyperglycemia, which can eventually lead to cardiovascular disease and diabetes mellitus. In the instant case, Applicants have identified an interesting set of compounds which might play a role in chronic inflammation associated to metabolic syndrome diseases, but essentially all of the work required to ultimately develop a treatment method (including clinical trials) has been left for others, since experimentation was not carried out with metabolic syndrome patients having chronic inflammation or pre-chronic inflammation and there is no evidence provided that such diseases such as cardiovascular disease and diabetes mellitus could actually be prevented from happening by the administration of the instant pharmaceutical compositions.

For the reasons discussed above, it would require undue experimentation for one skilled in the art to use the claimed methods.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 10-16 and 18 are rejected under 35 U.S.C. 102(b) as being anticipated by Gottlieb (US 4,468,379, cited in the IDS of 11/07) as evidenced by Chibret (US 5,000,936).

Gottlieb teaches the use of purified leukocyte dialysate subfraction (e.g., abstract; Examples 1-5) has anti-inflammatory properties (e.g., column1, lines 25-38; column 13, lines 50-54; column 22, lines 1-45). Gottlieb teaches treating suppression and prevention of contact dermatitis, which is an inflammatory disease due to exposure of a person to liquids or vapors containing organic solvents or hydrocarbon fuels or to environmental toxins (Examples 12-13) and which is inherently a 'chronic inflammatory disease' as taught by Chibret: "Contact dermatitis is an acute or chronic inflammation, often sharply demarcated, produced by substances in contact with the skin" (e.g., column 9, lines 57-60). The limitations of claim 1: "associated with the Metabolic Syndrome", claim 112: wherein said patient has at least one component of the

Metabolic Syndrome" and claims 13, 15, 16: "wherein the symptom is a proinflammatory state" (i.e., a component of the metabolic syndrome) are inherent to contact dermatitis. The limitation of claim 14: "mitigating a symptom characteristic of an inflammation-related metabolic disturbance" is inherent to treating contact dermatitis as taught by Gottlieb (Examples 12-13). The limitation of claim 18: "

Therefore, the reference is deemed to anticipate the instant claims above.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gottlieb (US 4,468,379, cited in the IDS of 11/07) in view of Chibret (US 5,000,936) and Hundal et al. (J Clin Invest, 2002, cited in the IDS of 11/07).

Gottlieb and Chibret are relied upon as above.

Hundal et al. teach use high-dose aspirin (a known anti-inflammatory substance) to treat chronic inflammation associated with the metabolic disease, ameliorating insulin resistance and improving glucose tolerance in patients having metabolic disease, such as diabetes type 2, (e.g., abstract). The limitation of claim 2: "wherein the chronic inflammation is evidenced by elevated C-reactive protein: is taught in page 1323, Table

1, last line. The limitation of claim 3: "elevated platelet count or platelet activity" is not expressly taught. The limitation of claim 4: "hypercholesterolemia" is taught, e.g., in page 1323, Table 1. The limitation of claim 6: "increased acute phase proteins including C-Reactive proteins" is taught, e.g., in page 1323, Table 1, last line. The limitation of claim 7: "diabetes mellitus", is taught, e.g., abstract and column 1, lines 1-2 The limitation of claims 8-9 "controlling elevated blood glucose level" is taught, e.g., Table 1, line 3. The limitation of claim 17: "deferring progression of a patient from diabetes" is taught, e.g., in abstract. The limitation of claim 18: "(b) monitoring the person for immune function response, inflammation and blood glucose level; and (c) continuing to administer to the patient said pharmaceutical preparation until the person shows a normal immune function response and normal measures of inflammatory parameters" is not expressly taught by Gottlieb.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method of use of the anti-inflammatory composition of Gottlieb by applying to chronic inflammation in diabetic metabolic disease patients as taught Hundal et al. The skilled artisan would have been motivated to do so because anti-inflammatory substances such as aspirin were found to treat chronic inflammation associated with the metabolic disease in diabetic patients, ameliorating insulin resistance and improving glucose tolerance in patients having metabolic disease, such as diabetes type 2, (e.g., abstract of Hundal et al.). There would have been a reasonable expectation of success, given that aspirin and leukocyte dialysate subfraction were known in the art to be anti-inflammatory substances and because

Gottlieb teaches using against chronic inflammation such as contact dermatitis. The adjustment of particular conventional working conditions (e.g., determining appropriate dosages and times of administration, measuring parameters for immune response, inflammation and blood glucose in the patients and selecting inflammatory conditions to be treated within such method) is deemed merely a matter of judicious selection and routine optimization that is well within the purview of the skilled artisan. As such, it would have been obvious to one skilled in the art at the time of invention to determine all optimum and operable conditions (e.g., dosages, times of administration, monitoring biological parameters of interest and selecting types of inflammation wherein the fraction is active), because such conditions are art-recognized result-effective variables that are routinely determined and optimized in the art through routine experimentation ("[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.". *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955). See MPEP 2145.05). One would have been motivated to determine all optimum and operable conditions in order to achieve the most effective and safest therapeutic methods, in the most efficient manner. One would have had a reasonable expectation for success because such modifications are routinely determined and optimized in the art through routine experimentation.

From the teaching of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention. Therefore, the invention as a whole was prima facie obvious to one of

ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary..

Conclusion

No claim is allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARCELA M. CORDERO GARCIA whose telephone number is (571)272-2939. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia J. Tsang can be reached on (571) 272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Marcela M Cordero Garcia/
Patent Examiner, Art Unit 1654

MMCG 05/08